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EXAMINER	
HELMS, LARRY RONALD	
ART UNIT	**PAPER NUMBER**
1642	

DATE MAILED: 01/31/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/063,518	EATON ET AL.	
	Examiner	Art Unit	
	Larry R. Helms	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-13 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-13 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 9/10/02.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-13 are pending and under examination.

Specification

2. The disclosure is objected to because of the following informalities: The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code on page 31, paragraph 205. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

Appropriate correction is required.

Information Disclosure Statement

3. The information disclosure statement submitted on 10 September 2002 has been considered by the examiner. However, since the Blast results cited therein are not true publications with a publication date, they are not fully in compliance with 37 CFR 1.97 and thus they will not be printed on the face of the patent issuing from this application.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

5. Claims 1-6, 9-10, 12-13 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claims 1-6, 9-10 comprise the limitations that the claimed protein lacks its associated signal peptide or comprises an "extracellular domain" optionally lacking its associated signal peptide. These limitations are indefinite because neither the figure (figure 14) nor the specification define or teach the metes and bounds of the extracellular domain. Further, if the protein has an extracellular domain, the recitation of "extracellular domain"..."lacking its associated signal sequence" is indefinite as a signal sequence is not generally considered to be part of an extracellular domain, as signal sequences are cleaved from said domains in the process of protein production in the cell. It is noted that Figure 14 provides no written description of the extracellular domain(s). As such, the metes and bounds of the now claimed fragments cannot be ascertained.

b. Claim 13 is indefinite for reciting "epitope tag" because the exact meaning of the phrase is not clear. Does the phrase mean an "epitope" where and antibody binds or a tag that allows for purification that is an amino acid sequence that does not require binding to an antibody, or some other tag?

Claim Rejections - 35 USC § 101

6. 35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1-13 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a substantial asserted utility or a well established utility.

Claims 1-13 are directed to isolated polypeptides that are 80-100% identical to SEQ ID NO:14 or full length or extracellular domain or sequences lacking the signal sequence as well as polypeptide encoded by the full-length of the cDNA deposited under ATCC 203579 and fusion proteins comprising such. The specification discloses the isolation of a nucleic acid, SEQ ID NO:13, which encodes a protein, SEQ ID NO:14 which is disclosed as PRO 1864 (see Figure 13 and 14). The DNA of SEQ ID NO:13 is disclosed to be over expressed in melanoma vs. normal skin but the protein is not disclosed to be expressed (see page 141).

The specification does not disclose that the polypeptide has any homology with known, characterized polypeptides. The instant specification does not disclose any additional information regarding PRO1864 such as subcellular location, timing of regulation during cellular differentiation, which hormones or transcription factors

regulate PRO1864, and what physiological significance PRO1864 plays. Therefore, it is a totally new, uncharacterized polypeptide with no well-established utility.

The specification generally asserts that all of the disclosed PRO polypeptides will be useful for a number of purposes, however, none of these asserted uses meet the three-pronged requirement of 35 U.S.C. § 101 regarding utility, namely, that the asserted utility be credible, specific and substantial. The asserted utilities will each be addressed in turn.

1) the PRO polypeptide can be used to isolate other polypeptides to which it binds (paragraph 0329): This asserted utility is not specific or substantial. Since the same can be done with any polypeptide, the asserted utility is not specific to the claimed PRO1864 polypeptides. Furthermore, since the specification does not disclose how PRO1864 or its binding partners can be used, significant further research would be required of the skilled artisan to determine how to use the claimed polypeptide or its binding partner. Since the asserted utility is not presented in a ready to use, real-world application, the asserted utility is not substantial.

2) the PRO polypeptide can be used as a molecular weight marker (paragraph 0334): This asserted utility is not specific. Since the same can be done with any polypeptide, the asserted utility is not specific to the claimed PRO1864 polypeptides.

3) the PRO polypeptide can be used in tissue typing (paragraph 0336): This asserted utility is not specific or substantial. With the exception of a few housekeeping genes, all polypeptides have a tissue specific pattern of expression, and thus virtually

any polypeptide can be used in tissue typing. Thus, the asserted utility is not specific to PRO1864.

4) the PRO polypeptide can be used in therapy (paragraph 0337): This asserted utility is not specific or substantial. Since a defect in any polypeptide is likely to cause a disease of some sort, every polypeptide is a target for drug development. Thus, the asserted utility is not specific to the claimed PRO1864 polypeptide. Furthermore, the specification does not disclose a nexus between any specific disease states and a change in amount or form of PRO1864. Significant further research would have to be conducted to identify such a nexus. Therefore, the asserted utility is not substantial.

5) the PRO polypeptide can be used to identify agonists or antagonists (paragraph 0345): Since the same can be done with any polypeptide, the asserted utility is not specific to the claimed PRO1864 polypeptides. Furthermore, since no activity has been assigned to PRO1864, the assays cannot be conducted until the specific biological activities of PRO1864 are determined empirically. Therefore, the asserted utility is also not substantial.

The specification also discloses that PRO1864 tested positive in a microarray analysis to detect over-expression of PRO polypeptides in cancerous tumors (Example 18, pp. 140). This information does not provide a credible, specific and substantial utility for PRO1864 nucleic acids, polypeptides or antibodies. PRO1864 mRNA levels are indicated as being over-expressed in melanoma tumor as compared to a normal skin. The data is not presented to indicate such overexpression or how it was determined. This is very vague, and does not disclose what mathematical calculations

were used to establish significance. Therefore, the data presented in the microarray assay are preliminary at best, and cannot be evaluated or repeated independently by the skilled artisan. Clearly, further research would be required of the skilled artisan to establish whether and how a probe used in the microarray assay could be used as diagnostic markers or therapeutic targets. Such further experimentation indicates that the asserted utility is not in currently available form.

Furthermore, the Literature indicates that such results are to be evaluated very critically. For example, Hu et al. (2003, Journal of Proteome Research 2:405-412) analyzed 2286 genes that showed a greater than 1-fold difference in mean expression level between breast cancer samples and normal samples in a microarray (p. 408, middle of right column). Hu et al. discovered that, for genes displaying a 5-fold change or less in tumors compared to normal, there was no evidence of a correlation between altered gene expression and a known role in the disease. However, among genes with a 10-fold or more change in expression level, there was a strong and significant correlation between expression level and a published role in the disease (see discussion section).

Finally, increased transcription does not always correlate with increased polypeptide levels. See Haynes et al. (1998, Electrophoresis 1921862-1871), who studied more than 80 proteins relatively homogeneous in half-life and expression level, and found no strong correlation between protein and transcript level. For some genes, equivalent mRNA levels translated into protein abundances, which varied more than 50-fold. Haynes et al. concluded that the protein levels cannot be accurately predicted from

the level of the corresponding mRNA transcript (p. 1863, second paragraph, and Figure 1). Therefore, the art indicates that it is not the norm that increased transcription results in increased polypeptide levels.

Thus, the proposed use of the PRO1864 polypeptides as diagnostic markers and therapeutic targets are simply starting points for further research and investigation into potential practical uses of the polypeptides. See Brenner v. Manson, 148 U.S.P.Q. 689 (Sus. Ct, 1966), wherein the court held that:

> "The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility", "[u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field", and "a patent is not a hunting license", "[I]t is not a reward for the search, but compensation for its successful conclusion."

8. Claims 1-13 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a credible, specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

9. Claims 1-5, 12-13 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

The claims are drawn to polypeptides having at least 80%, 85%, 90%, 95% or 99% sequence identity with a particular disclosed sequence. The claims do not require that the polypeptide possess any particular biological activity, nor any particular conserved structure, or other disclosed distinguishing feature. Thus, the claims are drawn to a genus of polypeptides that is defined only by sequence identity.

To provide evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of compete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the only factor present in the claim is a partial structure in the form of a recitation of percent identity. There is not even identification of any particular portion of the structure that must be conserved. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

Vas-Cath Inc. v. Mahurkar. 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the ad to recognize that he or she) invented what is claimed." (See Vas-Cath at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the

encompassed genus of polypeptides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is pad of the invention and reference to a potential method of isolating it. The compound itself is required. See Fiers v. Revel, 25 USPQZd 1601 at 1606 (CAFC 1993) and Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 18 USPQZd 1016.

One cannot describe what one has not conceived. See Fiddes v. Baird, 30 USPQZd 1481 at 1483. In Fiddes, claims directed to mammalian FGF'S were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only isolated polypeptides comprising the amino acid sequence set forth in SEQ ID NO:14, but not the full breadth of the claim meets the written description provision of 35 U.S.C. § 112, first paragraph. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 U.S.C. § 112 is severable from its enablement provision (see page 1115).

10. Claims 1-6, 11-13 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to provide an adequate written description of the invention and failing to provide an enabling disclosure without complete evidence either that the claimed biological materials are known and readily available to the public or complete evidence of the deposit of the biological materials.

The specification lacks complete deposit information for the deposit of the cell line containing cDNA deposited under ATCC accession No. 203579. It is not clear that the cDNA deposited as ATCC no. 203579 is known and publicly available or can be reproducibly isolated from nature without undue experimentation or is the same as SEQ ID NO:13 or encodes SEQ ID NO:14 or contains additional sequences in addition to SEQ ID NO:14.

Applicant's referral to the deposit of the cDNA on page 121 of the specification is an insufficient assurance that the required deposit has been made and all the conditions of 37 CFR 1.801-1.809 met.

If the deposit is made under the provisions of the Budapest Treaty, filing of an affidavit or declaration by applicant or assignees or a statement by an attorney of record who has authority and control over the conditions of deposit over his or her signature and registration number stating that the deposit has been accepted by an International Depository Authority under the provisions of the Budapest Treaty and that all restrictions upon public access to the deposited material will be irrevocably removed upon the grant of a patent on this application. This requirement is necessary when deposits are made

under the provisions of the Budapest Treaty as the Treaty leaves this specific matter to the discretion of each State.

If the deposit is not made under the provisions of the Budapest Treaty, then in order to certify that the deposits comply with the criteria set forth in 37 CFR 1.801-1.809 regarding availability and permanency of deposits, assurance of compliance is required. Such assurance may be in the form of an affidavit or declaration by applicants or assignees or in the form of a statement by an attorney of record who has the authority and control over the conditions of deposit over his or her signature and registration number averring:

(a) during the pendency of this application, access to the deposits will be afforded to the Commissioner upon request:

(b) all restrictions upon the availability to the public of the deposited biological material will be irrevocably removed upon the granting of a patent on this application:

(c) the deposits will be maintained in a public depository for a period of at least thirty years from the date of deposit or for the enforceable life of the patent of or for a period of five years after the date of the most recent request for the furnishing of a sample of the deposited biological material, whichever is longest; and

(d) the deposits will be replaced if they should become nonviable or non-replicable.

If a deposit is made after the effective filing date of the application for patent in the United States, a verified statement is required from a person in a position to corroborate that the biological material described in the specification as filed is the same as that deposited in the depository, stating that the deposited material is identical to the biological material described in the specification and was in the applicant's possession at the time the application was filed.

Applicant's attention is directed to In re Lundak, 773 F.2d. 1216, 227 USPQ 90 (CAFC 1985) and 37 CFR 1.801-1.809 for further information concerning deposit practice.

11. Claims 1-5, 12-13 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is undue include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The claims are drawn to a polypeptides having at least 80% amino acid sequence identity to the polypeptide of SEQ ID NO:28 or the extracellular domain thereof. There is no functional limitation in the claims as far as to the polypeptide. Applicants have taught the polypeptide consisting of the extracellular domain or, more accurately, the mature form of SEQ ID NO:14. The specification discloses the polynucleotide is overexpressed in melanoma tumor as compared to a normal skin. The specification does not teach that the polypeptide is over expressed in any disease state and the specification does not teach an activity for the polypeptide or any active regions of the polypeptide. Thus one would not know if the polypeptide with the claimed homology would function as a polypeptide of SEQ ID NO:14.

The claim encompasses an unreasonable number of inoperative polypeptides, which the skilled artisan would not know how to use. There are no working examples of polypeptides less than 100% identical to the polypeptide SEQ ID NO:14 or the mature form thereof. The skilled artisan would not know how to use non-identical polypeptides on the basis of teachings in the prior art or specification. Even if the claimed polypeptides had a function, the specification does not provide guidance for using polypeptides related to (*i.e.,* 80%-99% identity) but not identical to SEQ ID NO:14. The claims are broad because they do not require the claimed polypeptide to be identical to the disclosed sequence and because the claims have no functional limitation.

It is well known in the art that even a single modification or substitution in a protein sequence can alter the proteins function. Protein chemistry is probably one of

the most unpredictable areas of biotechnology. For example, the replacement of a single lysine at position 118 of the acidic fibroblast growth factor by a glutamic acid led to a substantial loss of heparin binding, receptor binding, and biological activity of the protein (see Burgess et al, Journal of Cell Biology Vol 111 November 1990 2129-2138). In transforming growth factor alpha, replacement of aspartic acid at position 47 with asparagine, did not affect biological activity while the replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen (see Lazar et al Molecular and Cellular Biology Mar 1988 Vol 8 No 3 1247-1252). Replacement of the histidine at position 10 of the B-chain of human insulin with aspartic acid converts the molecule into a superagonist with 5 times the activity of nature human insulin. Schwartz et al, Proc Natl Acad Sci USA Vol 84:6408-6411 (1987). Removal of the amino terminal histidine of glucagon substantially decreases the ability of the molecule to bind to its receptor and activate adenylate cyclase. Lin et al Biochemistry USA Vol 14:1559-1563 (1975).

These references demonstrate that even a single amino acid substitution or what appears to be an inconsequential chemical modification, will often dramatically affect the biological activity of the protein.

The specification does not disclose that the protein is overexpressed in any disease state, the specification states that the DNA of SEQ ID NO:13 is over expressed in melanoma vs normal skin. Those of skill in the art recognize that expression of mRNA, specific for a tissue type, does not necessarily correlate nor predict equivalent levels of polypeptide expression. In fact, evidence abounds in which protein levels do

not correlate with steady-state mRNA levels or alterations in mRNA levels. For example, Fu et al (EMBO Journal, 1996, Vol. 15, pp. 4392-4401) teach that levels of p53 protein expression do not correlate with levels of p53 mRNA levels in blast cells taken from patients with acute myelogenous leukemia, said patients being without mutations in the p53 gene. Further, Powell et al (Pharmacogenesis, 1998, Vol. 8, pp. 411-421, abstract) teach that mRNA levels for cytochrome P450 E1 did not correlate with the level of corresponding protein, and conclude that the regulation of said protein is highly complex. Vallejo et al (Biochimie, 2000, vol. 82, pp. 1129-1133, abstract) teach that no correlation was found between NRF-2 mRNA and protein levels suggesting post-transcriptional regulation of NRF-2 protein levels. These references serve to demonstrate that the analysis of levels of polynucleotide transcripts cannot be relied upon to anticipate levels of protein expression. In addition, Pennica et al (PNAS 95:14717-22, 1998) teach that the copy number is amplified but the RNA expression is actually reduced. Further, Jang et al (Clinical and Experimental Metastasis, 1997, vol. 15, pp. 469-483, abstract) teach that further studies are necessary to determine if changes in protein levels track with changes in mRNA levels for metastasis associated genes in murine tumor cells, thus providing further evidence that one of skill in the art cannot anticipate that the level of a specific mRNA expressed by a cell will be paralleled at the protein level due to complex homeostatic factors controlling translation and post-translational modification.

Thus, the predictability of protein translation and its possible utility as a diagnostic are not necessarily contingent on the levels of mRNA expression due to the

multitude of homeostatic factors affecting transcription and translation. Therefore, absent evidence of the protein's expression including the correlation to a diseased state, one of skill in the art would be unable to predictably use the polypeptides in any diagnostic setting without undue experimentation.

In view of the lack of guidance, lack of examples, and lack of predictability in the art and using the myriad of derivatives encompassed in the scope of the claims, one skilled in the art would be forced into undue experimentation in order to practice the broadly claimed invention.

Conclusion

12. No claim is allowed.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Larry R. Helms, Ph.D, whose telephone number is (571) 272-0832. The examiner can normally be reached on Monday through Friday from 6:30 am to 4:00 pm, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew, can be reached at (571) 272-0787.

14. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center. The faxing of such papers must conform with the notice published in the Official Gazette,

1096 OG 30 (November 15, 1989). The Fax Center telephone number is 571-273-8300.

Larry R. Helms

571-272-0832